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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/023,483	02/13/1998	JEFFREY A. HEROUX	2528-2	6994

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EXAMINER	
TUNG, JOYCE	
ART UNIT	**PAPER NUMBER**
1637	24

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/023,483	Applicant(s) Heroux et al.
	Examiner Joyce Tung	Art Unit 1637

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Jul 30, 2002* .

2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-61* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-61* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. Claims 1-61 are pending, claim 15 is newly amended and claims 41-61 are newly added.

2. Claims 1-14 and 16-40 remain rejected and the newly amended claim 15 is rejected under 35 U.S.C. §112, first paragraph as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention as the invention as set forth of pg 2-3 of the Office action mailed 7/30/2002.

and claims 1-14, 16-40 remain rejected and the newly amended claim 15 is rejected under 35 U.S.C. §112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention as set forth on page 3 of the Office action mailed 7/30/2002.

Applicants' arguments have been carefully considered and are not deemed persuasive as discussed below. Applicants argue that MPEP section 2163.02 supports the introduction of claim limitations that do not have literal support in the specification as originally filed. In particular applicants' point to the use of the term "[T]hreshold" in example 10 at page 21 of the specification, and specific recitation concerning the presence of 100pg DNA as the level which WHO considers negligible. To the matter of the MPEP, a complete recitation of the section under discussion indicated that support for terminology not in the specification as filed-- involving a departure from the application as filed will result in a rejection under section 112. Here clearly

the use of threshold is not that which applicants intend from the introduction of the limitation into the claims.

The subject matter of the claim need not be described literally (i.e., using the same terns or in *Haec verba*) in order for the disclosure to satisfy the description requirement. If a claim is amended to include subject matter, limitations. or terminology not present in the application as filed, involving a departure from, addition to, or deletion from the disclosure of the application as filed, the examiner should conclude that the claimed subject matter is not described in that application. This conclusion will result in the rejection of the claims affected under 35 U.S.C. 112, first paragraph-description requirement, or denial of the benefit of the filling date of a previously filed application, as appropriate. See MPEP 2163 for examination guidelines pertaining to the written description requirement.

Wherein applicants argue that they are allowed to be their own lexicographer it is under how defining their own meanings and limitation to terms excuses the applicants from providing the clear metes and bounds of the claims. Here the specification appears silent as to the use of 5 pg as the detection limit with 100pg set as the threshold limit value.

Furthermore, the threshold limitation, even when considered in view of the WHO information does not indicate that volume from in which the 100 pg is considered as a threshold. Simply 100 pg contamination in a liter is clearly distinct from a decaliter. For these reasons are maintained or newly applied as set forth in the preamble of the rejection.

3. Applicant's arguments with respect to the rejection of claims 1-40 under 35 U.S.C. 103 (a) over Hartley (5,043,272) in view of Eberle et al. (5,413,906) and in view of Wu et al. (Genomics, 1989, vol. 4, pg. 560-569) and Respess (5,599,662) have been considered but are moot in view of the new ground(s) of rejection.

NEW GROUNDS OF REJECTIONS

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claim 58 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Since the claim language "said total amount of nucleic acid contamination

comprises two or more different nucleic acid species of unknown sequence" has not supported in the specification, it constitutes the new matter.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

7. Claims 1-3, 6-12, 14-25, 28-32 and 34-37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hartley (5,043,272) in view of Eberle et al. (5,413,906) and Merrick et al. (Biotech Forum Europe, 1992, vol. 9(6), pg. 398-403).

Hartley discloses a random amplification method and kit using a random oligonucleotide primer in which the method uses at least one primer (see column 5, lines 10-24), which may be substituted with biotin (see column 6, lines 39) which is detectable species; having promoter site for RNA polymerase which is binding species; attached to a solid phase through using a linker (see column 9, lines 35), and at least one dNTP used in the method (see column 10, lines 5). There are also capture probe to capture the amplified products on magnetic beads (see column 12, lines 13 and 40-43). The primer is 8 bases long preferred and other length such as 4-mer, 5-mer can be used (see column 6, lines 19-24). The polymerase is Klenow fragment of DNA polymerase I (see column 4, lines 60). The reaction mixture contains pH 6.8, 400uM of the final concentration of dNTP, 5mM of magnesium and 10mM of 2-mercaptoethanol which is a reduce agent (See column 10, lines 1-8). The reaction contains at least one dNTP (see column 4, lines 27-30).

Hartley dose not disclose one dNTP which has binding species or detectable species.

Eberle et al. disclose a method for determining polymerase activity in which a detectable labeled mononucleotide triphosphate and immobilizable nucleoside triphosphate binding to a solid support are used (see column 2, lines 27-49, column 3, lines 50-68 and column 4, lines 1-21).

AS discussed in the response filed 10/11/2002, Applicants argue that Hartley does not disclose the method which is used in measuring the amount of a specific nucleic acid, not total

nucleic acid and the total amount of the nucleic acid contamination in the sample, the newly found reference, Merrick et al. disclose threshold assays for monitoring the purification of a product, for example, the determination of total DNA as contaminant in recombinant products (See pg. 399, column 2 to pg. 400, column 1, first paragraph) and the assay was applied to quantify for picogram amounts of total DNA, such as 2 pg of DNA can be detected in a nonradioactive format (See pg. 399, column 2 to pg. 400, column 1, first paragraph). Thus, it would have been prima facie obvious for one of ordinary skill in the art at the time of the instant invention to modify the method of Hartley et al. by applying the system of Merrick et al. with a detectable labeled mononucleotide triphosphate and immobilizable nucleoside triphosphate binding to a solid support as taught by Eberle et al. in the amount of Mg optimized. The motivation is that the system of Merrick et al. has the advantage of sensitivity, speed and quantitation to enable rapid optimization and validation of bioprocessing (See pg.399, column 3, second paragraph), the method of Hartley is for amplifying nucleic acid without prior knowledge of the sequence and it does not require complex handling or repeated intervention on the part of the technician performing the method (see column 9, lines 5-13) and the method of Eberle et al. provides a quick, simple more reliable and sensitive test (see column 2, lines 27-30). Thus it would have been prima facie obvious to carry out the method as claimed.

8. Claims 4, 5, 13, 26, 27,33, and 39-40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hartley (5,043,272) in view of Merrick et al. (Biotech Forum Europe, 1992,

vol. 9(6), pg. 398-403), Wu et al. (Genomics, 1989, vol. 4, pg. 560-569) and Respess (5,599,662).

The teachings of Hartley and Merrick et al. are set forth in section 7 above.

Hartley dose not disclose using a ligase and the labeled primer having binding species in the method.

Wu et al. disclose a ligase amplification system used as an allele-specific detection with T4 DNA ligase (see pg. 561, first column, 2nd paragraph).

Respess discloses a method which involves an improved primer which is biotin labeled and has binding species. Since the amplified products hybridize to a bound probes, it indicates that there are binding species on the primer (see column 12, lines 29-31).

The teachings of Wu et al. and Respess suggest instant claims 4, 5, 13, 26, 27 and 33 in which a random primer labeled and having binding species is used and a ligase is involved. The ligase is listed in instant claims 13 and 33.

One having ordinary skilled artisan in the art would have been motivated to combine these references at the time when the invention was made to get reasonable expectation of success because the method of Hartley is for amplifying nucleic acid without prior knowledge of the sequence and it does not require complex handling or repeated intervention on the part of the technician performing the method (see column 9, lines 5-13), the improved primer of Respess also more specifically amplifies a target without the simultaneous amplification of non-target

sequences (see column 1, lines 58-67 and column 2, lines 1-4) and the method of Wu involves a ligase for allele- specific detection, the system of Merrick et al. has the advantage of sensitivity, speed and quantitation to enable rapid optimization and validation of bioprocessing (See pg.399, column 3, second paragraph). It would have been prima facies obvious to carry out the method as claimed.

9. Claim 38 is rejected under 35 U.S.C. 103(a) as being unpatentable over Hartley (5,043,272) in view of Kozlowski et al. (6,096,499) and Merrick et al. (Biotech Forum Europe, 1992, vol. 9(6), pg. 398-403).

The teachings of Hartley and Merrick et al. are set forth in paragraph 7.

Hartley dose not disclose using one nucleotide which has at least one second label.

Kozlowski et al. disclose an invention to modulate mammalian DNA primase activity (See column 3, lines 7) involving a DNA polymerase α for the further extension of the products of the DNA primase which can be useful to enhance the signal incorporation of labeled nucleotide (See column 5, line 44-52) using distinct label (See column 6, lines 42-55). There are a first labeled nucleotide having a first label incorporated in polynucleotide produced from template-directed polynucleotide synthesis and a second labeled nucleotide having a second label which can be distinguished from the first label of the nucleotide species (See column 6, lines 42-55).

The teachings of Hartley and Kozlowski et al. suggested the limitations of claim 38 in which a random primer at least 4 nucleotides in length and having first label is mixed, at least one nucleotide triphosphate having at least one second label, polymerase are added at a condition for polymerase chain reaction and then measure total nucleic acid in a sample. Although Kozlowski et al. do not disclose measuring a total nucleic acid in a sample in which a random primer with a first label to label nucleotide is used, Hartley discloses using a random oligonucleotide primer in which the method uses at least one primer (see column 5, lines 10-24) (recited in instant claims 38), which may be substituted with biotin (see column 6, lines 39) which is detectable species. This suggests that a nucleotide sequence is labeled. Kozlowski et al. disclose using labeled nucleotide having distinct labels (See column 6, lines 42-55). A labeled ribonucleotide species has a first label and a deoxyribonucleotide species is labeled with a differentiable label, i.e. a differentiable label can be quantitatively distinguished from the first label by a conventional art-known technique (See column 7, lines 43-50).

One having ordinary skilled artisan in the art at the time of the instant invention would have been motivated to combine the teachings of two references to modify the method of Hartley by adding at least one nucleotide with a second label because the method of Hartley is for amplifying nucleic acid without prior knowledge of the sequence and it does not require complex handling or repeated intervention on the part of the technician performing the method (see column 9, lines 5-13) with a biotin labeled primer (see column 6, lines 39) which would have

been used by one having ordinary skill in the art for labeling a first label in a nucleotide sequence and the method might be desirable in the quantification of the amplification product (See column 6, lines 39-43) and the method of Kozlowski et al. involves using a differentially labeled nucleotide which will be quantitatively distinguished from the first label by a conventional art-known technique (See column 7, lines 43-50) and the method will be used for measuring the production of a nucleic acid molecule (See column 29, lines 6-12) and the system of Merrick et al. has the advantage of sensitivity, speed and quantitation to enable rapid optimization and validation of bioprocessing (See pg.399, column 3, second paragraph). It would have been prima facies obvious to carry out the method as claimed.

10. Claims 41-57 and 59-61 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hartley (5,043,272).

The teachings of Hartley et al. are set forth in section 7, above. Hartley does not disclose that the method is for determining the amount of total nucleic acid contamination in a sample as recited in the preamble of claims 41-45. Nevertheless, Hartley discloses that the method might be desirable in the quantification of the amplification product (See column 6, lines 42-43) and the amplified product is HPV 18 DNA (See column 10, lines 51-67) at picogram amount (See column 13, lines 11-21). HPV 18 DNA can be considered as a contamination in a sample. It would have been prima facie obvious to carry out the method as claimed.

11. Claims 58 is rejected under 35 U.S.C. 103(a) as being unpatentable over Hartley (5,043,272) as applied to claims 41-57 and 59-61 above, and further in view of Caskey et al. (5,364,759).

The teachings of Hartley et al. are set forth in section 7, above. Hartley does not disclose that the method is applied to quantify the total nucleic acid contamination which comprises two or more different nucleic acid species.

Caskey et al. disclose multiplex polymerase chain reaction for simultaneously performing PCR on greater than two different sequences (See column 6, lines 34-37).

Therefore, it would have been prima facie obvious for one of ordinary skill in the art at the time of the instant invention to apply the method of Hartley et al. to quantify the nucleic acid contamination which has two or more nucleic acid species because Caskey et al. disclose the method to do it (See column 6, lines 34-40).

12. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37

CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

13. Any inquiries concerning this communication or earlier communications from the examiner should be directed to Joyce Tung whose telephone number is (703) 305-7112. The examiner can normally be reached on Monday-Friday from 8:00 AM-4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached at (703) 308-1119 on Monday-Friday from 10:00 AM-6:00 PM.

Any inquiries of a general nature or relating to the status of this application should be directed to the Chemical/Matrix receptionist whose telephone number is (703) 308-0196.

14. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Art Unit 1637 via the PTO Fax Center located in Crystal Mall 1 using (703) 305-3014 or 308-4242. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989).

Joyce Tung

November 6, 2002

GARY BENZION
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600